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`Scary' Case Raises Doubts For HIV Vaccine

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BARCELONA, Spain -- The only way to end the AIDS epidemic is with a preventative vaccine. But a sobering and fascinating case study of one Boston patient, which quickly became the talk of the XIV International AIDS Conference here, suggests that making such a vaccine might be much more difficult than previously thought.

What happened was this: The immune system of the Boston patient was suppressing the AIDS virus for several months, even though the man wasn't taking any drugs -- a rare but not-unheard-of event. Blood tests showed that his immune system had mounted exactly the kind of robust and powerful attack against HIV that many researchers hope to elicit with a vaccine.

But then the man had unprotected sex -- he told his partner that he was HIV-positive, researchers say -- and got infected with a second strain of HIV. Even though his immune system was controlling the original HIV strain, it was unable to control the second strain, which is now running rampant in his body.

Some researchers fear that what befell this man, known by his research code AC06, could happen to someone who gets vaccinated against one strain of HIV but gets exposed to another strain. HIV is one of the most mutable viruses known to humanity -- far more variable than the influenza virus, for example -- so the chance of encountering strains different from a vaccine strain is very high. Scientists have classified HIV into at least 10 broad subtypes, and within those subtypes there are countless strains.

The case study also raises questions about one of the main approaches to developing an AIDS vaccine, one that has generated strong enthusiasm and is being pursued by drug makers Wyeth and Merck & Co., the National Institutes of Health, the International AIDS Vaccine Initiative, and Emory and Yale universities. This approach doesn't stimulate antibodies, like most other vaccines, but another arm of the immune system called killer T-cells.

The scientist who presented the study, Bruce Walker of Harvard Medical School in Boston, cautioned that "we can't draw broad conclusions from a single case." Other researchers, such as Emilio Emini, who is heading Merck's high-profile AIDS vaccine effort, agreed. Dr. Emini presented test-tube research suggesting that immune responses generated by Merck's vaccine are active against divergent HIV strains.

But Ronald Desrosiers, a veteran HIV vaccine researcher who is also from Harvard, described Dr. Walker's research as a "huge blow to vaccine development."

Purely by chance, Dr. Walker's colleagues -- Marcus Altfeld, Todd Allen, and Xu Yu -- had selected the Boston patient for special immunological and virological evaluation. For a year before he got infected with the second strain, they had been collecting a vast archive of laboratory tests and blood samples, which made it possible to provide remarkable detail on his case.

"It's one of the most important talks I've heard here from a scientific perspective," said John Moore, a vaccine researcher at the Weill Medical College of Cornell University in New York. "It's extremely scary."

In addition to the questions it raises for vaccine research, the case underscores the need for infected people to practice safe sex even with partners who are also infected, said Dr. Walker.

Scientists had debated whether it was possible for "superinfection" -- the scientific term for reinfection on top of an existing infection -- to occur with HIV. Many HIV-positive people believed that because they were already infected, no harm could come from unprotected sex with another HIV-positive person. But the new

study shows that a person can get infected with a strain that is worse for the patient. It is possible that a patient could even acquire a drug-resistant strain, undermining drug therapy.

In most patients, HIV is present at high levels in the blood, which causes them to progress to full-blown AIDS. But there have always been a lucky few "long-term nonprogressors" whose immune systems suppress the virus for years. Dr. Walker studied one patient who has been controlling his virus for more than 20 years.

Dr. Walker and others noted that such patients mount very strong immune responses against the virus, particularly by marshaling killer T-cells, which destroy cells that HIV has infected. Dr. Walker calls these cells the infantry, and notes that they need generals to direct them -- cells called CD4 helper T-cells, so named because they "help" mobilize the immune-system's attack. But these helper T-cells are precisely the ones that HIV usually wipes out, leaving the all-important infantry cells leaderless and unable to fight the virus effectively. Somehow, many long-term nonprogressors maintain their helper T-cells, which, in turn, keep their killer T-cells mobilized against HIV.

Dr. Walker thought that if patients could be treated within weeks or even days after they got infected, before HIV decimated the helper T-cells, then maybe these patients would also be able to keep HIV in check.

Six years ago, a young German man was, in fact, treated very early in the course of his infection by physician Heiko Jessen in a study being conducted by researcher Franco Lori. The so-called Berlin patient took himself off drugs, and his immune system kept the virus in check. Dr. Walker, who helped analyze the Berlin patient's immune system, was inspired to conduct a study to see if he could reproduce what happened in the Berlin patient. Patient AC06 was in that trial.

When he first went off drugs, patient AC06 only controlled the virus for a short period and had to go back on drugs. But when he stopped drugs a second time, his immune system was able to suppress HIV. Indeed, he had the kind of immune responses that Merck and other vaccine developers hope to induce. Specifically, he had high levels of killer T-cells that were able to detect and attack HIV at different points -- what scientists call "broad" immunity. But it didn't protect patient AC06 from the second strain.

"We did not anticipate that," said Dr. Walker.

Of course, an infected patient who has mounted an immune response is different from an uninfected vaccinated patient. HIV does damage, even if treated swifly, so patient AC06 did not have "a pristine, clean immune system," said Dr. Emini.

What's more, researchers would have a hard time detecting patients whose immune systems had rebuffed a second strain of the virus, for the simple reason that they wouldn't get infected. So it is possible that patient AC06 is a fluke, an example of a very rare event that just happened to occur while under observation. "To leap from this one patient to saying that this is the end of the vaccine business is really crazy," said Wayne Koff, the scientific leader of the International AIDS Vaccine Initiative.

But other scientists said the case study raises questions about the vaccine strategy of stimulating killer T-cells. Most traditional vaccines work by stimulating antibodies, which snare virus that is floating free in the bloodstream. One experimental vaccine, made by VaxGen Inc. of Brisbane, Calif., stimulates antibodies and is nearing completion of large efficacy trials. If the vaccine works, it would be a huge breakthrough. Even if it is only partially effective, it could help lead to better vaccines.

But many scientists say they believe VaxGen's experimental vaccine and others like it won't work. They say it has been very hard to find antibodies that neutralize a broad range of HIV strains. To date, no more than five such antibodies have been identified, each in only one person. The goal is to figure out a way to induce those antibodies, or ones similar to them, in most people.

The International AIDS Vaccine Initiative has launched a new consortium of top researchers to tackle this problem. One of them, Dennis Burton of the Scripps Research Institute in La Jolla, Calif., is working with some of the rare broadly neutralizing antibodies to do what he called in a talk here "reverse vaccinology." He identifies where those antibodies bind to HIV, and then characterizes the molecular structure of that part of the virus. He then hopes to alter that structure in such a way that the body will produce even better antibodies. Such work, however, will take years.

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